

BONE METABOLISM IN CEREBRAL PALSY AND THE EFFECT OF LIGHT-EMITTING DIODE (LED) IRRADIATION

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In recent years, through the availability of examination by bone metabolism markers, diagnosis and treatment for osteoporosis in elderly people has been greatly advanced. However, bone metabolism in cases of cerebral palsy has not been fully examined. Though children with cerebral palsy tend to be susceptible to insufficiency fractures, a method of treatment for insufficiency fractures has not been established. In the longitudinal progress of bone metabolism, although there was a difference depending on the severity, reduced bone resorption tended to be mild but osteogenesis tended to decrease in the severe cases. Osteogenesis and bone resorption markers decreased at around ages 8 and 15. The bone resorption marker maintained mild advancement after age 15.

With LED irradiation, all of IGF-1, ucOC, osteogenic marker; BAP, and urinary bone resorption marker; NTx/Cr showed a tendency to normalize. In particular, IGF-1, BAP, and NTx/Cr increased significantly one month after irradiation, compared to the non-irradiation group. Bone density assessed by the DIP method showed no apparent change in the short term either. Irradiation by a commercial LED light bulb indicated a possible positive effect on bone metabolism for children with severe cerebral palsy.

Key words: light emitting diode: LED, Cerebral palsy, bone metabolism, insufficiency fracture

Introduction

Children with severe cerebral palsy could have insufficiency fractures while undergoing daily care, or with convulsive seizures and the like, even when no force is applied. Injury resulting from a failure to recognize insufficiency fractures may be considered medical malpractice, leading to a possible lawsuit (**Figs.1a,1b**). Yet bone metabolism for cerebral palsy cases has not been well reviewed.

In recent years, bisphosphonates that inhibit

bone resorption are recognized as useful for elderly people's high-turnover osteoporosis, for which the bone resorption marker has been developed. However, experiments have clarified that the bone resorption inhibitor does not improve decreased bone formation at the diaphysis of a long bone by load reduction, ¹⁾ and a method of treatment for fragilitas ossium in severe cases has not been established.

In this study, bone density and bone metabolism of children with cerebral palsy were examined longitudinally. The possible effects of the use of commercial LEDs for bone metabolism were assessed for severely disabled children.

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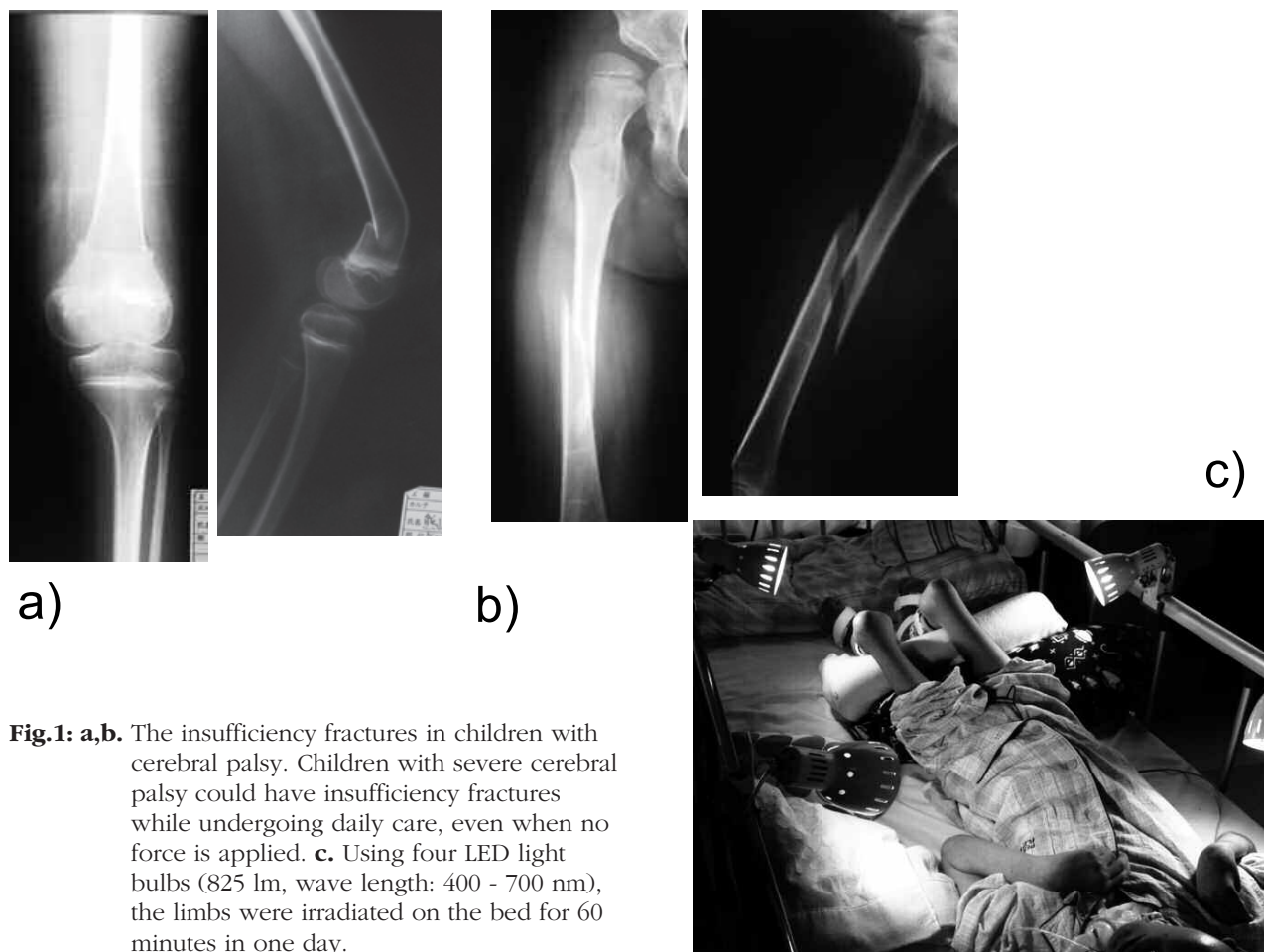


Fig.1: a,b. The insufficiency fractures in children with cerebral palsy. Children with severe cerebral palsy could have insufficiency fractures while undergoing daily care, even when no force is applied. **c.** Using four LED light bulbs (825 lm, wave length: 400 - 700 nm), the limbs were irradiated on the bed for 60 minutes in one day.

Subjects and Methods

Bone metabolism in cerebral palsy

The subjects were 131 cases with cerebral palsy (GMFCS Level III: 24; Level IV: 30; and Level V: 77); male: 84; female: 47; age: 2 to 27 (mean: 9 years old). Annual examination was conducted mainly measuring metacarpal bone density by the digital image processing (DIP) method, osteogenic marker: bone alkaline phosphatase (B-ALP), and urinary bone resorption marker: Type I collagen cross-linked N-telopeptide (NTx). The progress of 1 to 12 years (mean: 3 years) was examined.

LED (light-emitting diode) irradiation: Irradiation power density of LED lamp was measured at Japan Medical Laser Laboratory. The LDA9DH everleds (100

V/9.2 W) LED lamp made by Panasonic Corp. was used (**Fig.2a**).

Measurement Method: For measuring instruments, the PD300-BB-SH sensor and NOVA indicator both made by Ophir Optonics Ltd. were used. The measurement distance was 300 mm from the top of the lamp to the plane on the concentric circle centered on the central axis of the lamp. The concentric circles measuring 100 mm, 200 mm, 300 mm and 400 mm in diameter were divided into 8 equal parts by straight lines. The optical power density at the intersection points between the straight lines and the circumferences and the central point was measured (**Fig.2b**). Since 33 measurement points were measured for each lamp, 132 points were measured in total with 4 lamps. The measurement environment was set as 20 - 25°C in temperature, 30 - 70% in humidity, dark ambient illuminance when measuring, and below 1 μ W in residual

Spectral power

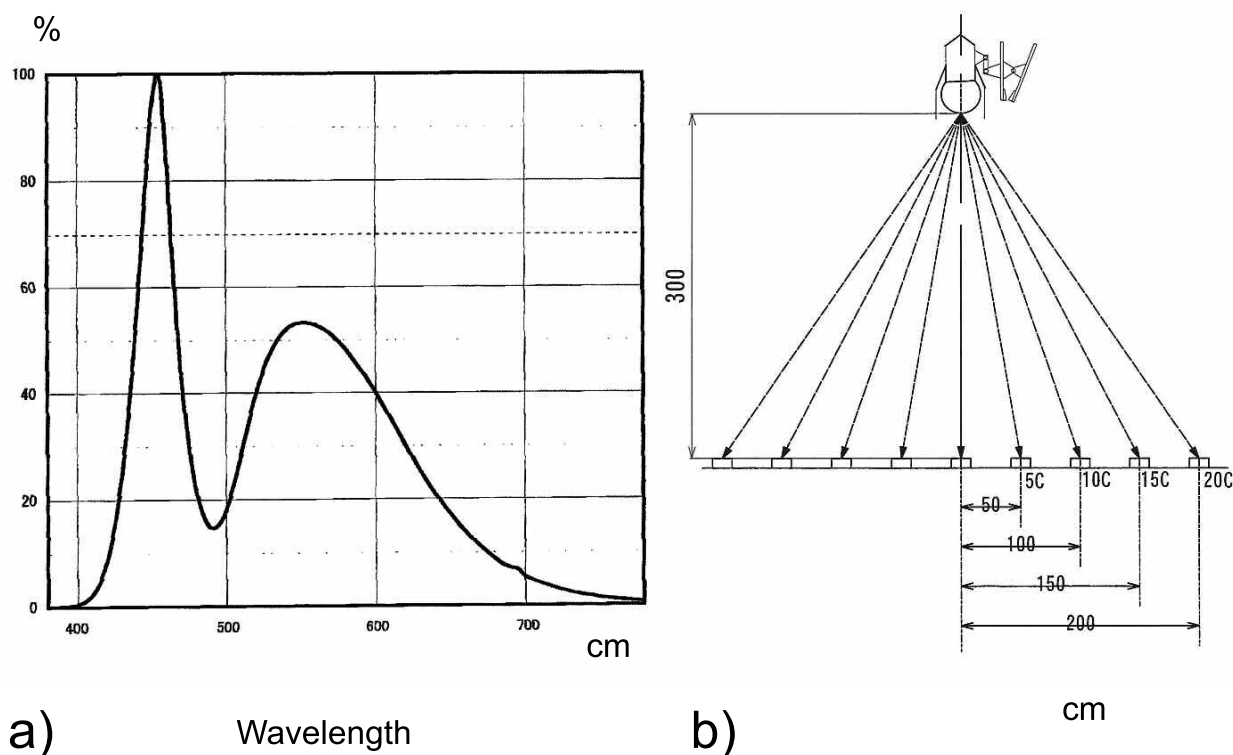


Fig.2: a. Relative spectral distribution of LDA9H everleeds. There is the peak in 446 - 477 nm of blue wavelength. **b.** The measurement distance was 300 mm from the top of the lamp to the plane on the concentric circle centered on the central axis of the lamp. The concentric circles measuring 100 mm, 200 mm, 300 mm and 400 mm in diameter were divided into 8 equal parts by straight lines.

light intensity.

Using four LED light bulbs (825 lm, wave length: 400 - 700 nm) for 8 cases, the limbs were irradiated on the bed for 60 minutes in one day (**Fig.1c**). After one month, intact PTH (parathyroid hormone), ucOC (undercarboxylated osteocalcin), IGF-1 (insulin-like growth factor-1), BAP, NTx serum, Homocystein, NTx urine, NTx/Cr, and bone density by the DIP method were measured to examine the effect on bone metabolism. Targeting 10 non-irradiated cases with a mean age of 13 years with decreased IGF-1, BAP, and NTx/Cr, effects on bone metabolism were examined as well. Also, the ages when insufficiency fractures occurred in our center were studied.

The studies were conducted based on the approval by the ethics board at Shinano Handicapped Children's Hospital and with the consent of the guardians for all cases.

Results

Bone metabolism in cerebral palsy

Nineteen cases of GMFCS Level V among the reduced bone density cases were followed up for more than 3 years using the DIP method. In the progress of bone density and bone metabolism for the older children, 3 cases that showed bone density to be extremely reduced and showed no longitudinal increase continued advancing bone resorption; 3 cases that showed no further bone density increase at around age 15 continued advancing bone resorption and decreased osteogenesis; 2 cases that showed bone density increase at around age 15 improved advanced bone resorption; and 11 cases that showed bone density to be low level but longitudinally increased mildly advanced bone resorption and mildly decreased osteo-

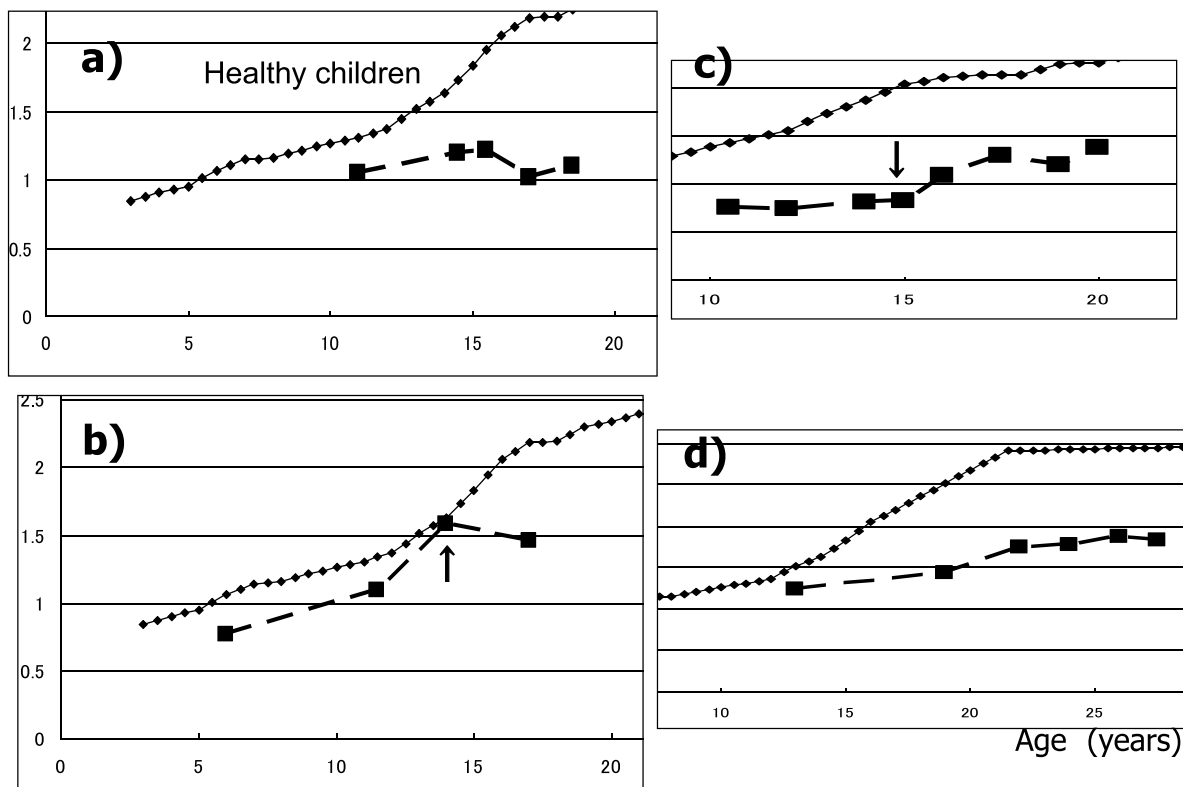
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Fig. 3: The progress of bone density and bone metabolism for the older children. **a.** 3 cases that showed bone density to be extremely reduced and showed no longitudinal increase continued advancing bone resorption. **b.** 3 cases that showed no further bone density increase at around age 15 continued advancing bone resorption and decreased osteogenesis. **c.** 2 cases that showed bone density increase at around age 15 improved advanced bone resorption. **d.** 11 cases that showed bone density to be low level but longitudinally increased mildly advanced bone resorption and mildly decreased osteogenesis.

genesis (**Figs.3a,3b,3c,3d**).

In the longitudinal progress of bone metabolism, although there was a difference depending on the severity, reduced bone resorption tended to be mild but osteogenesis tended to decrease in the severe cases. Osteogenesis and bone resorption markers decreased at around ages 8 and 15. The bone resorption marker maintained mild advancement after age 15 (Figs.4a,4b). In addition, in bone metabolism, cases were observed in which both bone resorption and osteogenesis had been decreasing since a younger age, and also cases in which only bone resorption had been reduced and suddenly osteogenesis decreased at around age 15. Also, as a factor to affect bone density and ossein, 16 cases of decreased IGF-1 associated

with bone growth and nutrition, and 17 cases of increased ucOC, an index of vitamin K shortage and ossein, were identified. Increased intact PTH, an index of vitamin D shortage, was observed as low in 3 cases. Homocysteine, an index of ossein, was at a normal level both pre- and post-irradiation, without obvious change.

Test results of power density per 1 second of LED lamp irradiation: Removed one lamp with extremely low power density due to a defective bulb, which was 0.85 - 0.94 mW/cm² (mean: 0.9 mW/cm²) on the optical axis. At 5 cm away from the optical axis, the mean was 0.85 mW/cm² (5% lower); at 10cm away, the mean: 0.73 mW/cm² (19% lower); 15 cm

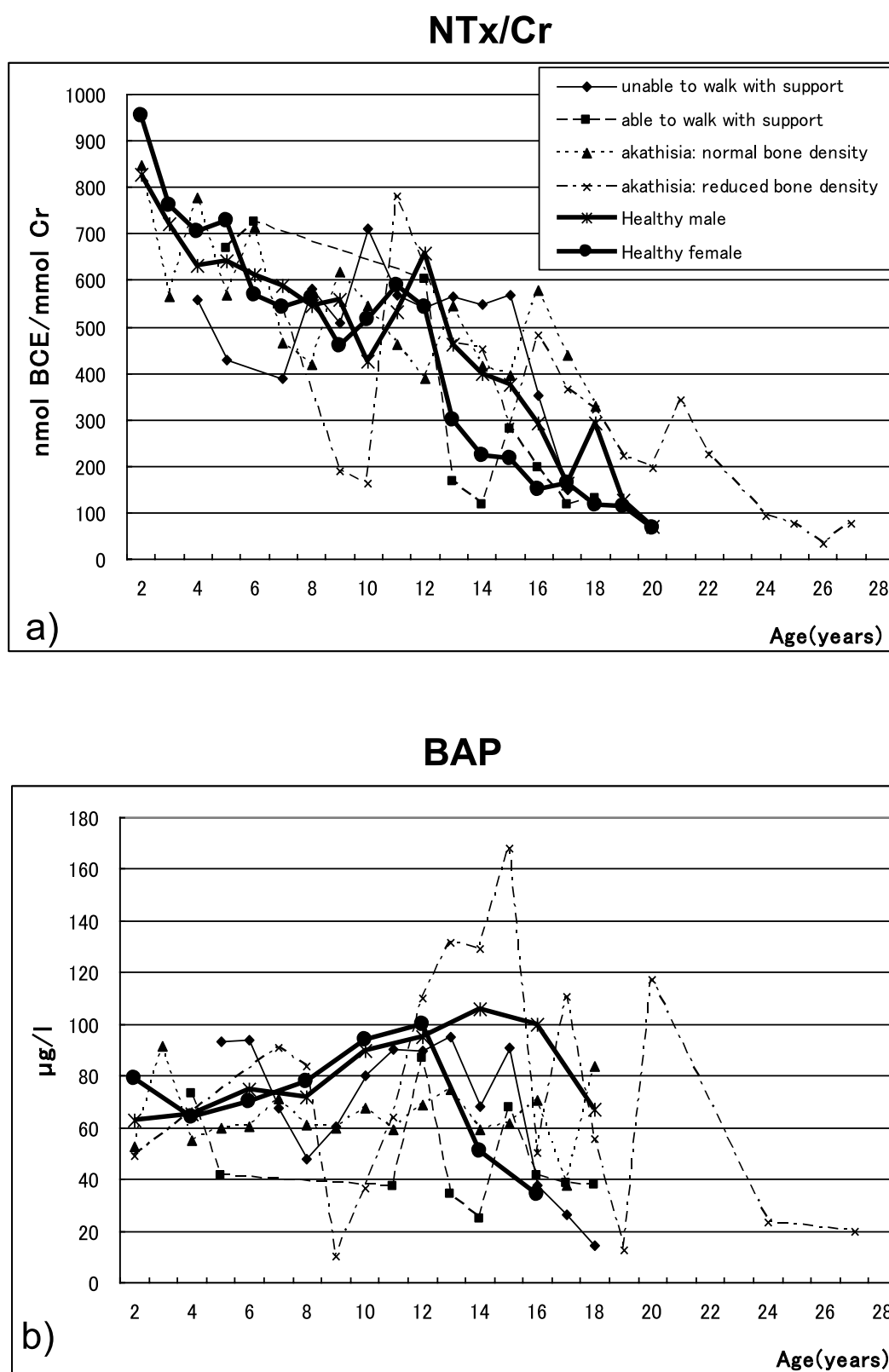


Fig. 4: a,b. In the longitudinal progress of bone metabolism, although there was a difference depending on the severity, reduced bone resorption tended to be mild but osteogenesis tended to decrease in the severe cases. Osteogenesis and bone resorption markers decreased at around ages 8 and 15. The bone resorption marker maintained mild advancement after age 15.

Table: Test results of power density per 1 second of LED lamp irradiation was 0.85 - 0.94 mW/cm² on the optical axis. At 5 cm away from the optical axis, the mean was 0.85 mW/cm²; at 10 cm away, the mean: 0.73 mW/cm²; 15 cm away, the mean: 0.58 mW/cm²; at 20 cm away, the mean: 0.44 mW/cm².

power density mW/cm ²				
lamp No distance mm	No1	No2	No3	average ± stdev.
0	0.9	0.85	0.94	0.9 ± 0.05
Φ 100	0.85 0.84 0.84 0.82 0.83 0.84 0.86 0.86	0.82 0.81 0.81 0.8 0.8 0.81 0.82 0.82	0.9 0.9 0.9 0.89 0.88 0.88 0.89 0.89	0.85 ± 0.04
Φ 200	0.73 0.72 0.71 0.69 0.69 0.72 0.76 0.75	0.7 0.7 0.7 0.69 0.67 0.69 0.71 0.72	0.78 0.79 0.8 0.77 0.76 0.76 0.77 0.77	0.73 ± 0.04
Φ 300	0.57 0.59 0.58 0.55 0.53 0.57 0.59 0.6	0.55 0.56 0.57 0.55 0.53 0.54 0.57 0.57	0.62 0.64 0.66 0.62 0.6 0.6 0.61 0.62	0.58 ± 0.03
Φ 400	0.43 0.43 0.45 0.43 0.4 0.42 0.44 0.46	0.42 0.43 0.44 0.42 0.39 0.4 0.43 0.42	0.48 0.49 0.51 0.47 0.45 0.46 0.46 0.48	0.44 ± 0.03

away, the mean: 0.58 mW/cm² (47% lower); at 20 cm away, the mean: 0.44 mW/cm² (51% lower) (**Table**).

With LED irradiation, 5 cases with low IGF-1 values were all increased (**Fig.5**). Three cases with low values on the osteogenic marker BAP increased, and 1 case with a high value decreased (**Fig.6**). Two cases with low values on the NTx/Cr urinary bone resorption marker increased, and 1 case with a high value decreased. The cases with normal values had no change (**Fig.7**). Five cases with low values on ucOC tended to increase and 1 case with high value tended to decrease (**Fig.8**). All the results indicated a tendency to normalize. In particular, IGF-1, BAP, and NTx/Cr increased significantly one month after radiation, compared to the non-irradiation group ($p < 0.05$). One month after end of irradiation, 1 case was observed

with a decrease in an abnormal value of mildly increased IGF-1 and an increase in an abnormal value of decreased urinary NTx/Cr (**Figs.5,7**). Bone density assessed by the DIP method showed no apparent change in the short period.

No adverse reaction occurred by the irradiation. One case experiencing frequent convulsive seizures stopped receiving irradiation and was removed from the group of subjects.

In our center, stages at which seriously disabled children fractured a long bone were at age 3 in 1 case; age 5, 1 case; age 6, 2 cases; age 7, 1 case; age 8, 2 cases; age 10, 2 cases; age 11, 1 case; age 9, 1 case; age 12, 1 case; age 13, 1 case; and age 18, 1 case. Eight out of 14 children (57%) were between 6 and 10 years old, showing higher occurrence.

Discussion

It is said that the frequency of insufficiency fractures is 7 - 9.7%/ year, ²⁾ and the risk factors such as being bedridden, medication (anticonvulsant), undernutrition, and lack of sunlight are known. But a method of treatment for bone fragility has not been established. ³⁾

Bone metabolism markers, as well as osteogenesis and bone resorption markers, tended to decrease markedly at around ages 8 and 15 in seriously disabled children. It is interesting that the decrease around 8 years old would be related to the stage of a fracture. Since NTx/Cr had daily variance and urine collection was often difficult with seriously disabled children, there were large fluctuations in value. However, NTx serum and BAP also had similar variations, with which a constant characteristic was thought to be shown.

Increase in 25(OH)VD was observed in the blood of serious cases with sun bathing. While it is very interesting how photic stimuli such as low level laser and LED affect bone metabolism, there has been no objective evaluation method and examinations have not been performed fully. We reported possibilities that low level laser would affect bone metabolism for seriously disabled children. ⁴⁾

It is said that the rays of the sun have a maximum of 100 mW/m² energy in the vicinity of Japan. In this study, there was 0.9 mW/m² of power density on the optical axis at 30 cm distance from the top of the lamp, meaning approximately 1% the power density compared to sun rays. However, because the power density was reduced to approximately 50% at 20 cm away, it was thought that the irradiation distance would become important.

The National Aeronautics and Space Administration

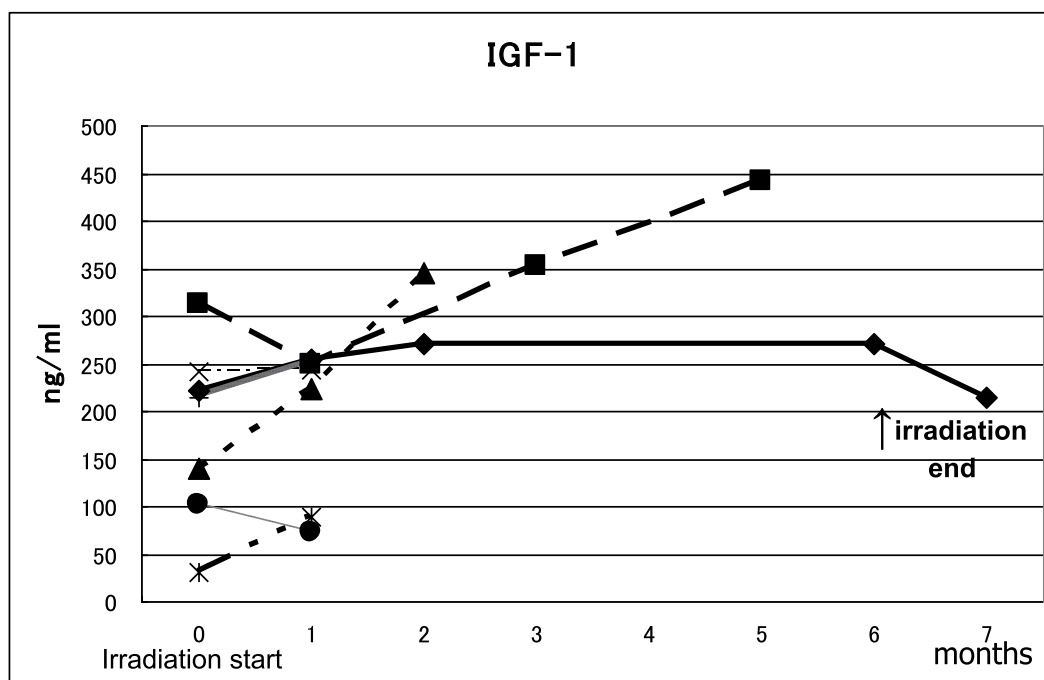


Fig. 5: Five cases with low IGF-1 values were all increased.

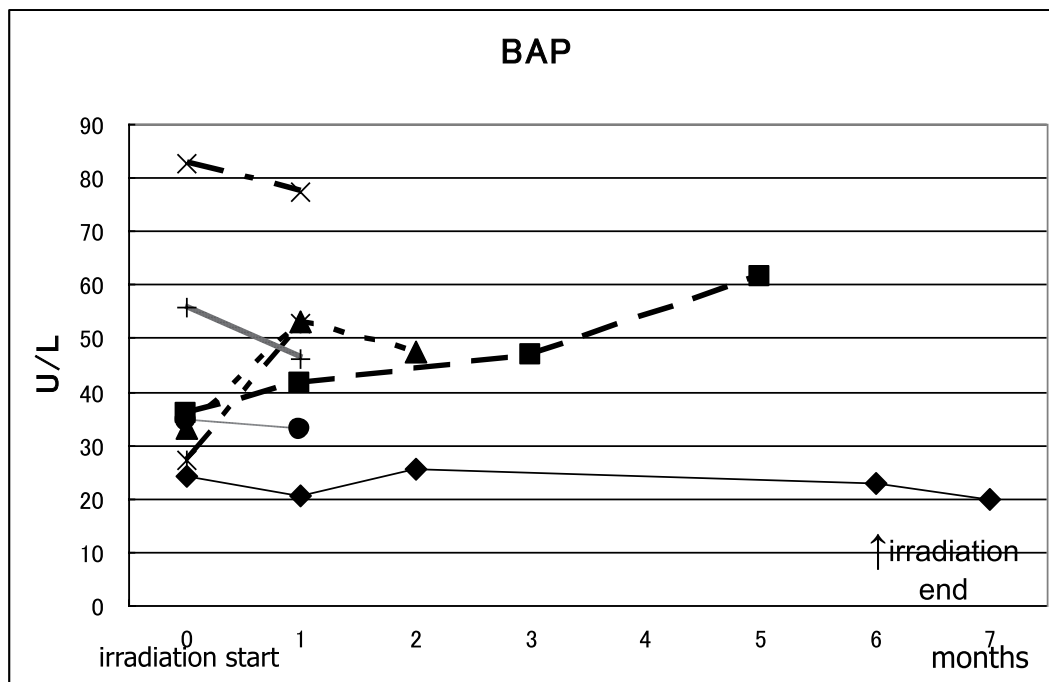


Fig. 6: Four cases with low values on the osteogenic marker BAP increased, and 1 case with a high value decreased.

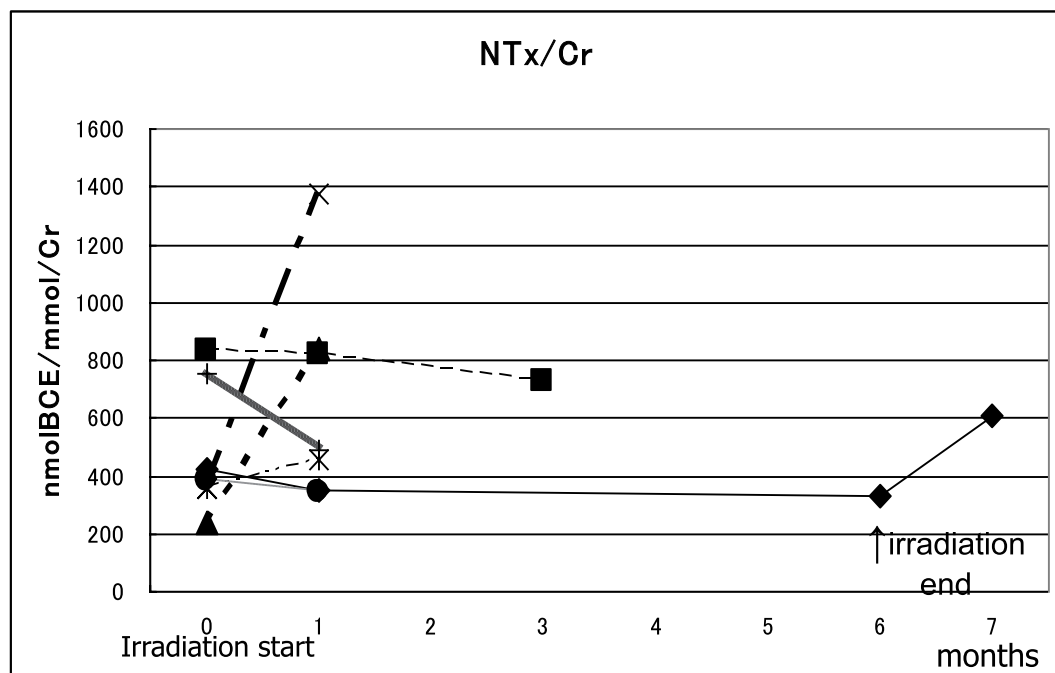


Fig. 7: Two cases with low values on the NTx/Cr urinary bone resorption marker increased, and 1 case with a high value decreased. The cases with normal values had no change.

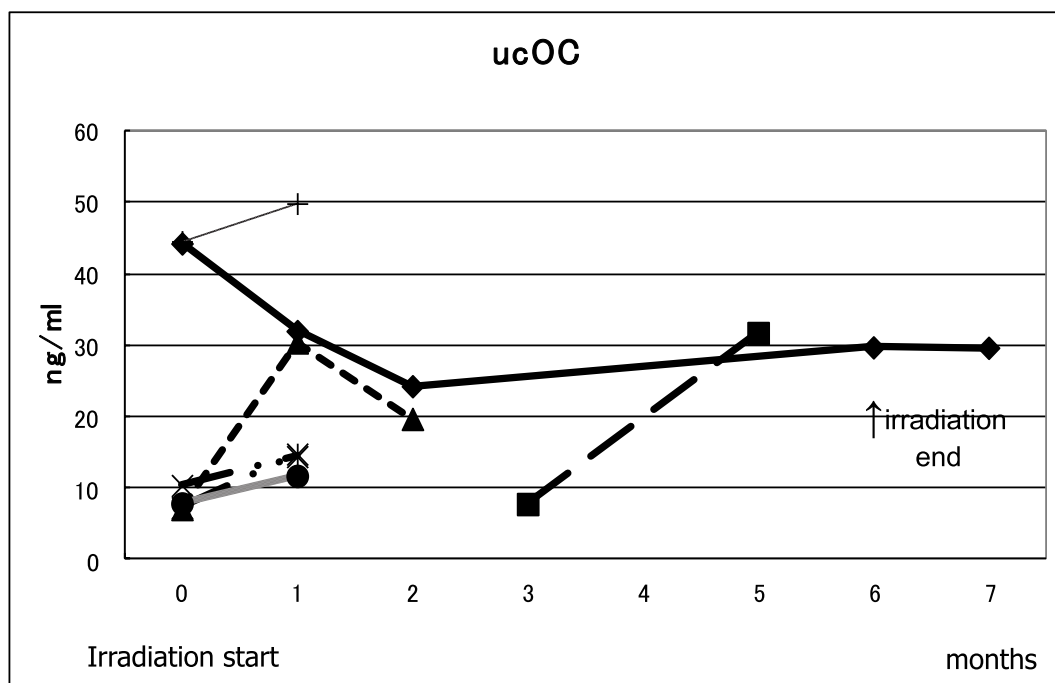


Fig. 8: Five cases with low values on ucOC tended to increase and 1 case with high value tended to decrease.

(NASA) is also aiming at LED which is biologically well-penetrating and able to irradiate larger areas than lasers, in the wound healing effect and the applications for muscle and bone atrophy for astronauts.⁵⁾

The characteristics of LED include easily obtaining a light that does not contain unnecessary ultraviolet or infra-red rays, as opposed to many light sources such as sunlight, fluorescent light, and incandescent light; LEDs are safer and more efficient than sun bathing. Though effects on organisms vary depending on the wavelength, we used LEDs with a wavelength characteristic in blue which is said to have a sedative effect in this study.

Conclusion

1) In the longitudinal progress of bone metabolism in cerebral palsy, although varied depending on the severity, bone resorption hardly decreased and osteogenesis tended to decrease in the severe cases. The osteogenesis and bone resorption markers

decreased around ages 8 and 15, and the bone resorption markers kept advancing mildly even after age 15.

- 2) By LED irradiation for one month, IGF-1 associated with osteogenesis, ucOC associated with osseins, BAP osteogenesis marker associated with bone density, NTx serum bone resorption marker, and urinary NTx/Cr tended to normalize.
- 3) In the cases that IGF-1, BAP and NTx/Cr decreased, they significantly increased one month after irradiation, compared to the non-irradiation group.
- 4) Irradiation by a commercial LED bulb can possibly have a beneficial effect on bone metabolism, and may become an inexpensive and safe at-home treatment method as a protection against insufficiency fractures for seriously disabled children.
- 5) LED irradiation could possibly become the world's first method of treatment for reduced bone density and insufficiency fractures in children with cerebral palsy who have had no method of treatment.

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